Remarks

Applicants note that in the June 18, 2003 Office Action, the Examiner states that claims 1-47 are pending, and in addition, applicants mistakenly stated in an Amendment submitted March 24, 2003 in connection with the above-identified application that claims 1-47 are pending. However, on reviewing the application, applicants note that the Preliminary Amendment filed January 2, 2001 in connection with the above-identified application, a copy of which is attached hereto as **Exhibit A**, canceled claims 1-4, 6-8, 10-16, 42, and 44-47. The receipt of the January 2, 2001 Preliminary Amendment by the United States Patent and Trademark Office is evidenced by a copy of the stamped returned postcard attached hereto as **Exhibit B**. Accordingly, applicants request entry of the January 2, 2001 Preliminary Amendment and, further, note that claims 5, 9, 17-41 and 43 should be the currently pending claims, with claims 17-41 withdrawn from consideration. Additionally, applicants have hereinabove amended claim 43. The amendments to claim 43 merely correct the claim dependency and applicants maintain that the amendments raise no issue of new matter. Accordingly, applicants request that this Amendment be entered after entry of the January 2, 2001 Preliminary Amendment.

Applicants further note that the claims pending and under examination after entry of the Preliminary Amendment, namely claims 5, 9, and 43, all fall within Examiner's Claim Group I, as elected by applicants in their March 24, 2003 Amendment in Response to February 24, 2003 Office Action in connection with the above-identified application. Finally, applicants request that the amendments to claims 1-4 detailed in the their March 24, 2003 Amendment in Response to February 24, 2003 Office Action be disregarded, as the March 24, 2003 amendments to claims 1-4

should not be entered in light of the Preliminary Amendment canceling claims 1-4.

Claim Objections

In the July 18, 2003 Office Action, the Examiner stated that claim 4 is objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In response, and in light of the Preliminary Amendment canceling claim 4 referred to in the "Remarks" section hereinabove, applicants note that this claim objection is now moot.

Claims Rejected Under 35 U.S.C. §112 (First Paragraph)

The Examiner stated that claims 1-2 rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response, and in light of the Preliminary Amendment canceling claims 1-2 referred to in the "Remarks" section hereinabove, applicants note that this claim rejection is now moot.

The Examiner stated that claims 42-47 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while

enabling for using the pharmaceutical compositions of the instant invention in an *in vitro* method, allegedly does not reasonably provide enablement for using the claimed pharmaceutical compositions *in vivo* for therapeutic purposes. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In response, and in light of the Preliminary Amendment canceling claims 42 and 44-47 referred to in the "Remarks" section hereinabove, applicants note that this claim rejection is now moot with respect to claims 42 and 44-47. With regard to claim 43, and to the extent the Examiner's rejection of claim 43 pertains to the currently amended claim 43, applicants traverse the rejection.

Applicants initially note that M.P.E.P. §2164.03 states that only a "reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity" is required for enablement. In addition, applicants note that the Examiner must give reasons for a conclusion of lack of correlation for an *in vitro* example (M.P.E.P. §2164.03). The Examiner cites Branch et al., stating that "internal structures of the targeted RNA molecules ….. can render target sites totally inaccessible *in vivo*". However, applicants have demonstrated bcl-xL antisense efficacy *in situ* - i.e. inside intact cells where the physical barriers mentioned by Branch et al. already exist (for example, see specification figures 9 to 17 inclusive). In addition, the antisense molecules claimed by applicants are clearly taken up by the cells as their exemplified efficacy demonstrates, and the references as cited by the Examiner do not state that such delivery does not work *in vivo*. Applicants further note that some of the very delivery

agents exemplified by applicants such as TAP and TMP (for example see page 21, lines 10-12, and figure 6) are mentioned by Jen et al. as effective in delivery to cell nuclei (see p 314, first paragraph). Furthermore, applicants note that it is well within the capabilities of one of ordinary skill in the art to perform routine dosage determination (which is sufficient for enablement, see M.P.E.P. §2164.01(c)).

Applicants further note that as stated in the application on page 35, lines 18-20, that the claimed active antisense, though they may vary in the extent they downregulate protein expression, all are active in the different cell lines regardless of delivery agent. Applicants also note that the therapeutic activity of the claimed oligonucleotides is defined by their sequence - control sequences do not work (see specification, page 22, lines 5-6). Different levels of inhibition does not preclude activity or usefulness. In fact, Crooke et al., cited by the Examiner, shows numerous examples of antisense with *in vivo* activity (see Table 1). Applicants further note that both PS and PO oligonucleotides downregulated bcl expression in differing cancer cell lines derived from bladder and prostate as shown in figures 9 to 17 inclusive. Moreover, applicants note that antisense treatment was determined by MTT assay to alone decrease cell viability (see page 36, lines 5-6).

Accordingly, applicants thus maintain that the rejected claims comply with the provisions of 35 U.S.C. §112, and request that the Examiner reconsider and withdraw this ground of rejection.

Double Patenting

The Examiner stated that claims 1-16 and 42-47 are provisionally rejected under the judicially created doctrine of double

patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending application No. 09/732,648, in view of Manoharan et al., Sanghvi et al., Matteucci et al., and Arnold et al. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application and the claims of the instant application are drawn to an antisense oligonucleotide or analog thereof comprising the nucleotide sequence according to SEQ ID NO:4.

In response, applicants note that of claims 1-16 and 42-47 rejected by the Examiner, only claims 5, 9, and 43 will be pending after entry of the January 2, 2001 Preliminary Amendment. Furthermore, claims 5, 9, and 43 were amended in the Preliminary Amendment filed January 2, 2001. As applicants have hereinabove requested that the January 2, 2001 Preliminary Amendment be entered, the double patenting rejection made by the Examiner in the June 18, 2003 Office Action becomes moot because the Examiner's arguments are premised on sequences not cited in the pending claims. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Peter J. Phillips
Registration No. 29,691
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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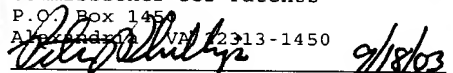


9/18/03
Peter J. Phillips Date
Registration No. 29,691

Dkt. 55669-A-PCT-US/JPW/EMW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Cy A. Stein
U.S. Serial No.	:	Not Yet Known (Continuation Application of PCT/US99/15250, filed 2 July 1999)
Filed	:	Herewith
For	:	OLIGONUCLEOTIDE INHIBITORS OF BCL-XL

1185 Avenue Of The Americas
New York, New York 10036
January 2, 2001

Assistant Commissioner for Patents
Washington, D. C. 20231
Box: Patent Application

Sir:

PRELIMINARY AMENDMENT TO THE ACCOMPANYING CONTINUATION APPLICATION FILED UNDER 37 C.F.R. §1.53

Applicants request that the following amendment be made in the above-identified application:

In the Specification:

On page 1, after the title, please delete the paragraph at lines 3-5 beginning "This application is a continuation-in-part..." and insert the following as a separate paragraph:

> --This application is a continuation of PCT International Application No. PCT/US99/15250, filed 2 July 1999, designating the United States of America, which is a continuation-in-part of U.S. Serial No. 09/109,614, filed July 2, 1998, the contents of which are hereby incorporated by reference into the present application.--

In the claims:

Please cancel claims 1-4, 6-8, 10-16, 42, and 44-47 without disclaimer or prejudice to applicant's right to pursue the subject matter of these claims in a future continuation or divisional application.

Please amend claims 5, 9, 17, 27, 37 and 43 as follows:

--5. (Amended) [The] An antisense oligonucleotide [of claim 3,] comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L, or M (SEQ ID NOS: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide.--

--9. (Amended) [The] An antisense oligonucleotide [of claim 3,] comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L, or M (SEQ ID NOS: 1-13), respectively, wherein one or more of the oligonucleotide's sugars contain an -OMe group at their 2' position.--

--17. (Amended) A method of treating cancer, comprising introducing into a tumor cell an effective amount of [the] an antisense oligonucleotide [of claim 16,] comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L, or M (SEQ ID NOS: 1-13), respectively, wherein the oligonucleotide comprises one or more bases with a C-5 propynyl pyrimidine modification, thereby reducing the levels of bcl-2 protein produced and treating cancer.--

--27. (Amended) A method of treating cancer, comprising introducing into a tumor cell an effective amount of [the] an antisense oligonucleotide [of claim 3,] comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L, or M (SEQ ID NOS: 1-13), respectively, thereby reducing the levels of bcl-xL protein produced and treating cancer.--

--37. (Amended) A method of promoting the regression of vascular lesions, comprising introducing into a vascular cell an amount of [the] an antisense oligonucleotide [of claim 3] comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L, or M (SEQ ID NOS: 1-13), respectively, effective to reduce the levels of bcl-xL protein produced, thereby promoting the regression of vascular lesions.--

--43. (Amended) [The] A pharmaceutical composition [of claim 42,] comprising an effective amount of an antisense oligonucleotide or analog thereof of claim 3 and a pharmaceutically acceptable carrier, wherein the effective amount is between 0.1 μM and 10 μM.--

REMARKS

This application is a continuation of PCT International Application No. PCT/US99/15250, filed 2 July 1999, designating the United States of America, which is a continuation-in-part of U.S. Serial No. 09/109,614, filed July 2, 2998. Accordingly, the

parent application, PCT International Application No. PCT/US99/15250, is pending today in the United States of America pursuant to 35 U.S.C. §363, and the subject continuation application is co-pending therewith in fulfillment of the provisions of 35 U.S.C. §120.

By this Preliminary Amendment, applicants have hereinabove amended the specification on page 1 to insert the continuation data. Applicants maintain that the amendments made hereinabove do not raise any issue of new matter. Accordingly, applicants respectfully request entry of the Amendment.

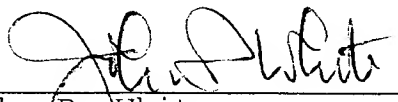
Claims 1-47 were pending in the subject application. By this Amendment, applicants have canceled claims 1-4, 6-8, 10-16, 42 and 44-47 without disclaimer or prejudice, and amended claims 5, 9, 17, 27, 37, and 43. Accordingly, upon entry of this Amendment, claims 5, 9, 17-41 and 43, as amended, will be pending.

Support for the amendments to claims 5, 9, 17, 27, 37 and 43 may be found inter alia in the specification, as originally-filed, at page 13, line 35 through page 14, line 2 and page 15, lines 1-3; page 13, line 35 through page 14, line 2 and page 15, lines 13-16; page 13, line 35 through page 14, line 2 and page 16, lines 22-27; page 13, line 35 through page 14, line 2 and page 17, lines 7-8; page 13, line 35 through page 14, line 2 and page 18, line 25 through page 19, line 1; and page 13, line 35 through page 14, line 2, page 19, lines 15-18 and page 19, lines 9-10, respectively, and in originally filed claim 3 upon which these claims originally depended. Applicants, therefore, maintain that the amendments herein to the specification and the claims do not raise any issue of new matter and respectfully request that this Amendment be entered.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the filing fee of $547.00, is deemed necessary in connection with this Preliminary Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

by placing your receiving date stamp hereon and returning to us.

Applicant Cy A. Stein SMR

Client CLMB.U.(0575) File No. 55669-A-PCT-US Atty. JPW/GJC

Date January 2, 2001

Kindly acknowledge receipt of the accompanying

New Patent Application of Cy A. Stein entitled OLIGONUCLEOTIDE INHIBITORS OF BCL-XL, continuation of PCT International Application No. PCT/US99/15250, International filing date 2 July 1999, including specification (38pp), claims (5pp), abstract (1p), formal drawings (figures 1-17, 22pp), 1 loose set of formal drawings (22pp), transmittal letter in triplicate, a Preliminary Amendment (5pp), a Declaration and Power of Attorney (unsigned) (3pp), a check in the amount of **$547.00**, and an Express Mail Certificate of Mailing bearing Label No. EK 873 630 415 US dated January 2, 2001

JC715 U.S. PTO
09/753169
01/02/01

DUE DATE: January 2, 2001

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